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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,139	11/20/2001	Mark Thiede	640100-420	9767

27162 7590 07/13/2007

CARELLA, BYRNE, BAIN, GILFILLAN, CECCHI,
STEWART & OLSTEIN
5 BECKER FARM ROAD
ROSELAND, NJ 07068

EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
07/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,139	THIEDE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 12, 2006 has been entered.

Claims 1-5, 9-27 are cancelled. Claim 6 is amended.

Claims 6-8 are under consideration

It is noted that the Examiner of record has changed.

Specification

Applicant's arguments, see page 1 of Applicant's response, filed December 26, 2006, with respect to sequence compliance have been fully considered and are persuasive. Applicant indicates that a sequence listing, amended page 18, a computer disk, and response have been submitted in response to an objection to sequence compliance. The objection of the specification has been withdrawn.

Withdrawn Rejections

35 U.S.C. § 101

Applicant's arguments, see Applicant's response, pages 3-4, filed August 2, 2006, with respect to the rejection of claims 6-8 have been fully considered and are persuasive. Applicant indicates that in the sheep tail wound study, cells that expressed human beta-2 microglobulin in the tail wound appeared in the dermis and dermal appendages and had the morphological appearance of fibroblasts consistent with participation in the wound healing response (Applicant's response, page 4, 3rd parag.). This is found persuasive as the study indicates that mesenchymal stem cells differentiate appropriately in tissues. The rejection of claims 6-8 has been withdrawn.

35 U.S.C. § 102

Applicant's arguments, see Applicant's response, page 3, filed August 2, 2006, with respect to the rejection of claims 6-8 as being anticipated by Diukman et al. have been fully considered and are persuasive. Applicant indicates that Diukman et al. do not teach administration of cells consisting essentially of mesenchymal cells to a fetus in utero. The rejection of claims 6-8 has been withdrawn.

Applicant's arguments, see Applicant's response, page 3, filed August 2, 2006, with respect to the rejection of claims 6-8 as being anticipated by Barnes et al. have been fully considered and are persuasive. Applicant indicates that Barnes et al. do not teach administration of cells consisting essentially of

mesenchymal cells to a fetus in utero. The rejection of claims 6-8 has been withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method of treating wounded sheep skin in utero comprising:

administering cells consisting essentially of human mesenchymal stem cells to a sheep in utero,

does not reasonably provide enablement for the full scope of

a method of engrafting mesenchymal stem cells from any species of animal comprising:

administering cells consisting essentially of mesenchymal stem cells to a fetus of any species in utero.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has provided a response indicating that the skin wounding example in the specification (page 24) is enabled and has utility. The Examiner has found this persuasive and has indicated a scope of enablement, as seen above. However, the claims are not enabled for its fullest breadth, which is discussed as follows. Response to Applicant's rebuttals, August 2, 2006, will be addressed following the rejection.

While the specification provides guidance for an artisan to treat wounded sheep skin in utero comprising administering cells consisting essentially of human mesenchymal stem cells (MSC) to sheep in utero, the specification does not enable an artisan to practice the claimed invention for its fullest breadth. As indicated in the previous Office Actions, neither the art nor the specification provides guidance for using chimeric organs (e.g., Office Action, October 28, 2005, page 4) and thus, the only context of the invention is that the MCS are used in therapy. The one example that the specification provides is in utero treatment of a wounded sheep tail using human MCS. However, this one example does not enable the full breadth of therapies encompassed by the claims. The specification indicates the intended uses from the claimed method: "1) large scale tissue engineering particularly for repair of musculoskeletal injury; 2) cellular therapy for diseases of mesenchymal origin such as muscular dystrophy, osteoporosis, osteogenesis imperfecta, and collagen disorders; 3) bone marrow conditioning to facilitate engraftment of autologous or allogeneic hematopoietic stem cells; and 4) gene therapy (specification, page 25)." However, post-filing art teaches that there are a number of problems that an

artisan must overcome before he or she is able to practice using mesenchymal stem cells routinely.

Flake, 2004, Best Practice and Research Clinical Obstetrics and Gynaecology, 18: 941-958, indicates that there are three assumptions that artisans fail to acknowledge and that these assumptions hinder the in utero use of stem cells in diseased tissues: 1) there is space available in the early gestational fetus for engraftment of transplanted cells without the need for ablation, 2) competition from normal host cells is not prohibitive to engraftment of donor cells, and 3) the fetal immune system is not a barrier to the engraftment of allogeneic or xenogeneic cells. In addition to these 3 assumptions, the art also teaches that because there is a lack of microenvironmental support for xenogenic cells, the number of transplanted cells is low (Flake, pages 944-947, under "Evidence Supportive of IUHCT").

Bianco et al., 2000, The Journal of Clinical Investigation, 105: 1663-1668, also teach that the precedent of hematopoietic transplantation has lead many to a simplistic view of stromal stem cells and their dependent tissues. While the widely known key principle of bone marrow transplantation (BMT) is the seed and soil paradigm, wherein upon ablation of a recipient marrow, progenitors infused via the circulation (the seed) can home into the non ablated marrow stroma (the soil) and regenerate a hematopoietic tissue, the principle relies on a few established biological properties of hematopoietic stem cells (HSCs) and their dependent hematopoietic lineages that do not apply to stromal progenitors and their dependent connective tissues (Bianco et al., page 1666, 2nd col., 1st parag.

under "Are marrow stromal stem cells systemically transplantable?"). To illustrate this point, Bianco et al. provides an example that treatment of skeletal diseases remains unlikely because of their inherent differences from HSCs. First, Bianco et al. indicate that systemic infusion of stromal stem cells is unlikely to treat skeletal diseases because of a stromal cell's inherent differences from hematopoietic stem cells (HSCs). While HSCs can replenish the whole hematopoietic system in a few weeks, building a whole adult skeleton requires 15 years. Further, while all HSCs need to do to replenish the hematopoietic system is generate cells, building a skeleton entails creating a complex physical structure whose precise spatial layout reflects an equally precise timing of events over a period of years (Bianco et al., page 1666, 2nd col., 2nd parag.). Second, with regard to the application of gene therapy in MSC, Bianco et al. teach that human stromal cells cannot yet be transduced with high enough efficiency to generate the required number of engineered cells. Further, proper regulation of expression of a desired gene in these cells is problematic and transgenes that express successfully in standard, continuous, or immortalized cell lines cannot be used directly for in vitro models using human cells, let alone for clinical applications (Bianco et al., page 1666, 1st col., 2nd parag. under "Marrow stromal stem cells and skeletal diseases"). As these teachings apply to the instant invention, while the specification, pages 21-24, indicates that human MSC differentiate according to the tissue they settle in and differentiated human cells were detected in the tail wound of sheep (specification, page 24), these results are not indicative that the method can be used in large scale tissue engineering,

cellular therapy, bone marrow conditioning, and gene therapy. Given that the sheep were healthy and that the number of transplanted cells were small, an artisan cannot extrapolate whether the transplanted human cells are able to treat any musculoskeletal diseases.

With regard to the specification indicating that the claimed method can be used in bone marrow conditioning (specification, page 25, 1st parag. 2nd point), the specification teaches that human MSC differentiate into CD23 positive cells (specification, page 23). However, this is not indicative that the bone marrow has been conditioned to facilitate engraftment of hematopoietic cells. With regard to the specification indicating that the claimed method can be used in gene therapy (specification, page 25, 1st parag. 4th point), Bianco et al. teach that transfecting stem cells cannot be achieved at high efficiency such that the cells can be used in therapeutic applications; the specification provides no guidance otherwise and thus, the invention is not enabled for this aspect. Finally, with regard to the scope of the claims being limited to treating sheep with human MSC, Flake indicates that beyond the sheep model of hematopoietic transplantation, results in other hosts, such as monkey, goat, rat, and mouse were not as successful (Flake, page 945, parag. 1-2). As this applies to the instant invention, the art indicates that one xenogenic transplant example is not indicative that other xenogenic transplants are enabled. As such, the enabled invention is limited to sheep as the host and human MSC.

Applicant's arguments filed August 2, 2006 have been fully considered and are persuasive in part.

Applicant indicates that a working example indicates that mesenchymal stem cells may be administered to a fetus in utero to repair damaged tissue. Thus, Applicant has demonstrated a utility for the claimed invention and has provided adequate guidance for a form of treatment practicing the method of engraftment as set forth broadly in the claims (Applicant's response, page 5, parags. 1-4). In response, as indicated above, the claimed invention has the indicated scope of enablement.

Applicant provides a response with regard to the Mackenzie and Santer-Nanan papers. Applicant indicates that when the entire Mackenzie paper is taken in context, Mackenzie has a reasonable expectation that different populations of mesenchymal stem cells can be implanted into fetuses in utero, whereby the mesnechymal stem cells would differentiate into various cells types in sufficient amounts, and then persist in the born animal for a sufficient amount of time in order to treat or counteract the effects of various diseases or disorders. In response, this is not persuasive. As described above, while human MCS can differentate in sheep following in utero transplantation, Mackenzie does not provide guidance for a) uses of chimeric organs (beyond that taught by the specification with regard to wound healing in the skin), b) that the number of MSC that differentiate are in sufficient numbers to treat other disease/disorders encompassed by the claims (e.g. musculoskeletal), and c) that other xenogenic transplants of MCS in utero can occur. As such, Mackenzie does not provide guidance that the artisan is enabled for the full breadth of the claimed invention. With regard to Santener-Nanan, Applicant indicates that the publication states

that, "(s)tem cells might have a great potential for tissue repair undertaken during the fetal and neonatal period." In response, Santer-Nanan's statement is an assertion and not evidence. It is also noted that Santer-Nanan indicates that there is potential that stem cells could be used for tissue repair and indicates that in 2005, the art has not indicated the method steps required to enable an artisan for its fullest breadth. Finally, it is noted that the post-filing teachings of Flake, 2004 and Bianco et al., 2000 indicate that the specification, at the time of filing was not enabled for its fullest breadth. As, such, the claims only remain enabled for its scope as described above.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Joanne Hama
Art Unit 1632